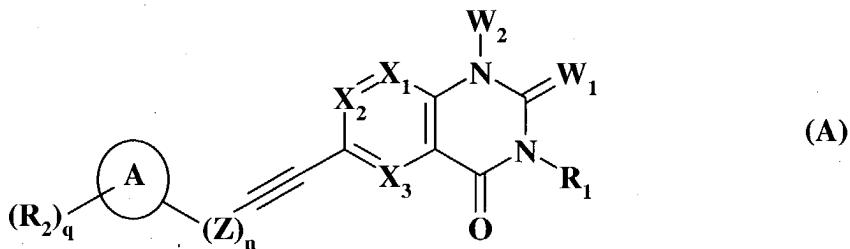


CLAIMS

What is claimed is:

1. A combination, comprising valdecoxib, or a pharmaceutically acceptable salt thereof, and an allosteric alkyne inhibitor of MMP-13 of Formula (A)



(A)

or a pharmaceutically acceptable salt thereof, or an N-oxide thereof,
wherein:

- 10 W1 is O, S, or NR3, wherein R3 is hydrogen, (C1-C6)alkyl, hydroxyl or cyano;
W2 is selected from :

hydrogen;
trifluoromethyl;
NH2;
15 (C1-C10)alkylN(H);
[(C1-C10)alkyl]2N, wherein each (C1-C10)alkyl moiety is the same or
different;
(C1-C6)alkyl;
(C3-C6)alkenyl;
20 (C3-C6)alkynyl;
phenyl;
naphthyl;
phenyl-(C1-C10)alkyl;
naphthyl-(C1-C10)alkyl;
25 (C3-C10)cycloalkyl-(C1-C10)alkyl;
an aromatic 5-membered or 6-membered monocyclic heterocycle
comprising carbon atoms and from 1 to 4 heteroatoms selected from O, S,
N(H), and N-(C1-C10)alkyl;

a nonaromatic 5-membered or 6-membered monocyclic heterocycle comprising carbon atoms and from 1 to 3 heteroatoms selected from O, S, N(H), and N-(C₁-C₁₀)alkyl;

5 wherein in W₂ each (C₁-C₁₀)alkyl, (C₁-C₆)alkyl, (C₃-C₆)alkenyl, (C₃-C₆)alkynyl, phenyl, naphthyl, phenyl-(C₁-C₁₀)alkyl, naphthyl-(C₁-C₁₀)alkyl, (C₃-C₁₀)cycloalkyl-(C₁-C₁₀)alkyl, aromatic heterocycle, and nonaromatic heterocycle group is independently unsubstituted or substituted by from 1 to 3 groups, which may be identical or different, selected from halo, NH₂, (C₁-C₁₀)alkylN(H), [(C₁-C₁₀)alkyl]₂N, wherein each (C₁-C₁₀)alkyl moiety is the same or different, cyano, trihalo(C₁-C₆)alkyl, (C₁-C₆)acyl, C(=O)OR₄, -OR₄, and SR₄;

R₄ is hydrogen or (C₁-C₆)alkyl; or

W₂ and W₁ may be taken together to form a diradical group W₂-W₁ of formula

W₃=X₄-N;

15 W₃ is N or CR₅ wherein R₅ is selected from:

hydrogen;

OR₆;

SR₆;

(C₁-C₆)alkyl;

20 (C₃-C₈)cycloalkyl;

a saturated heterocycle comprising from 3 to 8 ring members which are carbon atoms and one heteroatom selected from O, S, N(H), and N-(C₁-C₁₀)alkyl;

phenyl;

25 naphthyl;

(C₅-C₁₀)heteroaryl comprising carbon atoms and from 1 to 4 heteroatoms selected from O, S, N(H), and N-(C₁-C₁₀)alkyl;

phenyl-(C₁-C₁₀)alkyl; and

naphthyl-(C₁-C₁₀)alkyl;

30 R₆ is selected from hydrogen, (C₁-C₆)alkyl, phenyl-(C₁-C₁₀)alkyl, and naphthyl-(C₁-C₁₀)alkyl;

wherein in W_3 each (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, saturated heterocycle, phenyl, naphthyl, (C_5-C_{10})heteroaryl, phenyl-(C_1-C_{10})alkyl, and naphthyl-(C_1-C_{10})alkyl group is independently unsubstituted or substituted by $(CH_2)_p-OH$ or $(CH_2)_p-NH_2$;

5 p is an integer of from 0 to 4 inclusive;

X_4 is N or CR₇, wherein R₇ is selected from:

hydrogen;

NR₈R₉;

OR₈;

10 SR₈;

(C_1-C_6)alkyl;

(C_3-C_8)cycloalkyl;

a saturated heterocycle comprising from 3 to 8 ring members which are carbon atoms and one heteroatom selected from O, S, N(H), and N-(C_1-C_{10})alkyl;

15 C₁₀ alkyl;

phenyl;

naphthyl;

(C_5-C_{10})heteroaryl comprising carbon atoms and from 1 to 4 heteroatoms selected from O, S, N(H), and N-(C_1-C_{10})alkyl;

20 phenyl-(C_1-C_{10})alkyl; and

naphthyl-(C_1-C_{10})alkyl;

R₈ and R₉ are the same or different, and are selected from hydrogen;

(C_1-C_6)alkyl; phenyl-(C_1-C_{10})alkyl; and naphthyl-(C_1-C_{10})alkyl;

wherein in X_4 each (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, saturated heterocycle,

25 phenyl, naphthyl, (C_5-C_{10})heteroaryl, phenyl-(C_1-C_{10})alkyl, and naphthyl-(C_1-C_{10})alkyl group is independently unsubstituted or substituted by $(CH_2)_p-OH$ or $(CH_2)_p-NH_2$, wherein p is an integer from 0 to 4 inclusive;

X_1 , X_2 and X_3 independently of each other are N or C-R, wherein R is selected from:

30 hydrogen;

(C_1-C_6)alkyl;

hydroxyl;

- (C₁-C₆)alkoxy;
halo;
trifluoromethyl;
cyano;
5 nitro;
S(O)_{n1}R₄, wherein R₄ is as defined above;
NR₁₀R₁₁;
n₁ is an integer of from 0 to 2 inclusive;
R₁₀ and R₁₁ are the same or different, and are independently selected from
10 hydrogen;
(C₁-C₆)alkyl;
phenyl-(C₁-C₁₀)alkyl; and
naphthyl-(C₁-C₁₀)alkyl; or
R₁₀ and R₁₁ may be taken together with the nitrogen atom to which they are
15 bonded to form a 5-membered or 6-membered ring containing carbon atoms,
the nitrogen atom to which R₁₀ and R₁₁ are attached, and optionally a second
heteroatom selected from O, S, N(H), and N(C₁-C₁₀)alkyl,
wherein not more than two of the groups X₁, X₂, and X₃ simultaneously are a
20 nitrogen atom;
n is an integer of from 0 to 8 inclusive;
Z is C(R₁₂)(R₁₃);
Each R₁₂ and R₁₃ independently of each other are selected from:
hydrogen;
(C₁-C₆)alkyl;
25 trihalo(C₁-C₆)alkyl;
halo;
NH₂;
(C₁-C₆)alkylN(H);
[(C₁-C₆)alkyl]₂N, wherein each (C₁-C₆)alkyl moiety is the same or
30 different;
OR₄;
SR₄; and

- C(=O)OR₄, wherein R₄ is as defined above; or
R₁₂ and R₁₃ on the same carbon atom may be taken together with the carbon atom to which they are attached to form a carbonyl group; and
Z can contain 1 carbon-carbon double bond when two R₁₂ groups are absent and n
5 is an integer of from 2 to 8; and
Z can contain 2 carbon-carbon double bonds when four R₁₂ groups are absent or three R₁₂ and one R₁₃ groups are absent and n is an integer of from 3 to 8; and
Z can contain 1 carbon-carbon triple bond when two each of R₁₂ and R₁₃ are absent and n is an integer of from 2 to 8; and
10 Z can contain 2 carbon-carbon triple bonds when four each of R₁₂ and R₁₃ are absent and n is an integer of from 4 to 8; and
One C(R₁₂)(R₁₃) group in Z can be replaced with O, N(H), N(C₁-C₆)alkyl, S, S(O), or S(O)₂;
A is selected from:
15 phenyl;
an aromatic 5-membered or 6-membered monocyclic heterocycle comprising carbon atoms and from 1 to 4 heteroatoms selected from O, S, N(H), and N-(C₁-C₁₀)alkyl;
a nonaromatic 5-membered or 6-membered monocyte comprising carbon atoms and from 0 to 4 heteroatoms selected from O, S, N(H), and N-(C₁-C₁₀)alkyl;
20 naphthyl;
an aromatic 8-membered to 12-membered bicyclic comprising two aromatic rings independently selected from 5-membered or 6-membered rings, wherein the rings may be the same or different and bonded or fused to each other, and wherein the bicyclic comprises carbon atoms and from 1 to 6 hetero atoms selected from O, S, N(H), and N-(C₁-C₁₀)alkyl;
25 an aromatic 8-membered to 12-membered bicyclic comprising one aromatic 5-membered or 6-membered ring and one non-aromatic 5-membered or 6-membered ring, wherein the rings may be bonded or fused to each other, and wherein the bicyclic comprises carbon atoms and from 0 to 6 hetero atoms selected from O, S, N(H), and N-(C₁-C₁₀)alkyl; and
30

a non-aromatic 8-membered to 12-membered bicyclic comprising two non-aromatic rings independently selected from 5-membered or 6-membered rings, wherein the rings may be the same or different and bonded or fused to each other, and wherein the bicyclic comprises carbon atoms and from 0 to 4 hetero atoms selected from O, S, N(H), and N-(C₁-C₁₀)alkyl;

5 Each R₂ may be the same or different, and is independently selected from:

- hydrogen;
- (C₁-C₆)alkyl;
- halo;
- 10 cyano;
- nitro;
- trihalo(C₁-C₆)alkyl;
- NR₁₀R₁₁;
- OR₁₄;
- 15 SR₁₄;
- S(O)R₁₄;
- S(O)₂R₁₄;
- (C₁-C₆)acyl;
- (CH₂)_kNR₁₀R₁₁;
- 20 X₅(CH₂)_kNR₁₀R₁₁;
- (CH₂)_kSO₂NR₁₄R₁₅;
- X₅(CH₂)_kC(=O)OR₁₄;
- (CH₂)_kC(=O)OR₁₄;
- 25 X₅(CH₂)_kC(=O)NR₁₄R₁₅;
- (CH₂)_kC(=O)NR₁₄R₁₅; and
- X₆-R₁₆;

X₅ is O, S, N(H), or N(C₁-C₆)alkyl;

k is an integer of from 0 and 3 inclusive;

R₁₀ and R₁₁ are as defined above;

30 R₁₄ and R₁₅ may be the same or different, and independently are hydrogen or (C₁-C₆)alkyl;

X₆ is a single bond, -CH₂-, O, or S, S(O), or S(O)₂;

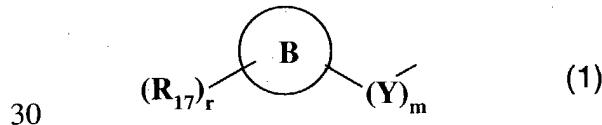
R₁₆ is selected from:

- phenyl;
- an aromatic 5-membered or 6-membered monocyclic heterocycle comprising carbon atoms and from 1 to 4 heteroatoms selected from O, S, N(H), and N-(C₁-C₁₀)alkyl;
- 5 cyclopentyl;
- cyclohexyl; and
- a nonaromatic 5-membered or 6-membered monocyclic heterocycle comprising carbon atoms and from 1 to 3 heteroatoms selected from O, S, N(H), and N-(C₁-C₁₀)alkyl;
- 10 wherein in R₁₆ each phenyl, aromatic 5-membered or 6-membered, heterocyclic ring, cyclopentyl, cyclohexyl, and non-aromatic 5-membered or 6-membered heterocyclic ring group independently is unsubstituted or substituted with from 1 to 3 groups independently selected from (C₁-C₆)alkyl, halo, trihalo(C₁-C₆)alkyl, hydroxyl, (C₁-C₆)alkoxy, SH, (C₁-C₆)alkylthio, NH₂, (C₁-C₆)alkylN(H), [(C₁-C₆)alkyl]₂N, wherein each (C₁-C₆)alkyl moiety may be 15 the same or different;

q is an integer of from 0 to 7 inclusive;

R₁ is a group selected from:

- 20 hydrogen;
- (C₁-C₆)alkyl;
- (C₃-C₆)alkenyl; and
- (C₃-C₆)alkynyl,
- wherein in R₁ each (C₁-C₆)alkyl, (C₃-C₆)alkenyl, and 25 (C₃-C₆)alkynyl group is independently unsubstituted or substituted with from 1 to 3 groups independently selected from NH₂, (C₁-C₆)alkylN(H), [(C₁-C₆)alkyl]₂N, wherein each (C₁-C₆)alkyl moiety may be the same or different, (C₁-C₆)alkyl, cyano, trihalo(C₁-C₆)alkyl, C(=O)OR₄, OR₄, SR₄, wherein R₄ is as defined above, and a group of formula (1)



m is an integer of from 0 to 8 inclusive,

Y is CR₁₈R₁₉;

Each R₁₈ and R₁₉ independently of each other, is selected from:

hydrogen;

5 (C₁-C₆)alkyl;

phenyl;

trihalo(C₁-C₆)alkyl;

halo;

NH₂;

10 (C₁-C₆)alkylN(H);

[(C₁-C₆)alkyl]₂N, wherein each (C₁-C₆)alkyl moiety may be the same or different;

OR₄;

SR₄; and

15 C(=O)OR₄;

R₄ is as defined above;

Y can contain 1 carbon-carbon double bond when two R₁₈ groups are absent and

m is an integer of from 2 to 8; and

Y can contain 2 carbon-carbon double bonds when four R₁₈ groups are absent or

20 three R₁₈ and one R₁₉ groups are absent and m is an integer of from 3 to 8; and

Y can contain 1 carbon-carbon triple bond when two each of R₁₈ and R₁₉ are absent and m is an integer of from 2 to 8; and

Y can contain 2 carbon-carbon triple bonds when four each of R₁₈ and R₁₉ are absent and m is an integer of from 4 to 8; and

25 One C(R₁₈)(R₁₉) group in Y can be replaced with O, N(H), N(C₁-C₆)alkyl, S, S(O), or S(O)₂;

B is a group selected from:

phenyl;

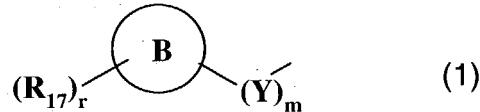
30 an aromatic 5-membered or 6-membered monocyclic heterocycle comprising carbon atoms and from 1 to 4 heteroatoms selected from O, S, N(H), and N-(C₁-C₁₀)alkyl;

- a nonaromatic 5-membered or 6-membered monocycle comprising carbon atoms and from 0 to 4 heteroatoms selected from O, S, N(H), and N-(C₁-C₁₀)alkyl;
- 5 naphthyl;
- an aromatic 8-membered to 12-membered bicyclic comprising two aromatic rings independently selected from 5-membered or 6-membered rings, wherein the rings may be the same or different and bonded or fused to each other, and wherein the bicyclic comprises carbon atoms and from 1 to 6 hetero atoms selected from O, S, N(H), and N-(C₁-C₁₀)alkyl;
- 10 an aromatic 8-membered to 12-membered bicyclic comprising one aromatic 5-membered or 6-membered ring and one non-aromatic 5-membered or 6-membered ring, wherein the rings may be bonded or fused to each other, and wherein the bicyclic comprises carbon atoms and from 0 to 6 hetero atoms selected from O, S, N(H), and N-(C₁-C₁₀)alkyl; and
- 15 a non-aromatic 8-membered to 12-membered bicyclic comprising two non-aromatic rings independently selected from 5-membered or 6-membered rings, wherein the rings may be the same or different and bonded or fused to each other, and wherein the bicyclic comprises carbon atoms and from 0 to 4 hetero atoms selected from O, S, N(H), and N-(C₁-C₁₀)alkyl;
- 20 r is an integer of from 0 to 7 inclusive,
- Each R₁₇ may be the same or different and independently is selected from:
- hydrogen;
- (C₁-C₆)alkyl;
- halo;
- 25 cyano;
- nitro;
- trihalo(C₁-C₆)alkyl;
- NR₁₀R₁₁;
- OR₁₄;
- 30 SR₁₄;
- S(O)R₁₄;
- S(O)₂R₁₄;

(C₁-C₆)acyl;
(CH₂)_kNR₁₀R₁₁;
X₅(CH₂)_kNR₁₀R₁₁;
(CH₂)_kSO₂NR₁₄R₁₅;
5 X₅(CH₂)_kC(=O)OR₁₄;
(CH₂)_kC(=O)OR₁₄;
X₅(CH₂)_kC(=O)NR₁₄R₁₅;
(CH₂)_kC(=O)NR₁₄R₁₅; and
X₆-R₁₆, wherein X₅, k, R₁₀, R₁₁, R₁₄, R₁₅, X₆, and R₁₆ are as defined above.

10 2. The combination of Claim 1, wherein:

W₂ is (C₁-C₆)alkyl;
W₁ is O; and
R₁ is a group of formula (1)



15 wherein Y, B, R₁₇, m, and r are as defined for Formula (A) in Claim 1.

3. The combination of Claim 1, wherein the compound of Formula (A) is selected from:

4-{6-[3-(4-methoxy-phenyl)-prop-1-ynyl]-1-methyl-2,4-dioxo-1,4-
20 dihydro-2H-quinazolin-3-ylmethyl}-benzoic acid methyl ester;
4-[1-methyl-2,4-dioxo-6-(3-phenyl-prop-1-ynyl)-1,4-dihydro-2H-
quinazolin-3-ylmethyl]-benzoic acid;
4-{6-[3-(4-methoxy-phenyl)-prop-1-ynyl]-1-methyl-2,4-dioxo-1,4-
dihydro-2H-quinazolin-3-ylmethyl}-benzoic acid;
25 4-{6-[3-(4-methoxy-phenyl)-prop-1-ynyl]-1-methyl-2,4-dioxo-1,4-
dihydro-2H-pyrido[3,4-d]pyrimidin-3-ylmethyl}-benzoic acid;
4-[1-methyl-2,4-dioxo-6-(3-phenyl-prop-1-ynyl)-1,4-dihydro-2H-
pyrido[3,4-d]pyrimidin-3-ylmethyl]-benzoic acid;

4-benzyl-7-(3-phenyl-prop-1-ynyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one;

4-benzyl-7-[3-(4-methoxy-phenyl)-prop-1-ynyl]-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one;

5 4-{7-[3-(4-methoxy-phenyl)-prop-1-ynyl]-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl}-benzoic acid methyl ester;

4-[5-oxo-7-(3-phenyl-prop-1-ynyl)-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl]-benzoic acid; and

10 4-(1-methyl-2,4-dioxo-6-(2-phenylethynyl)-1,4-dihydro-2H-quinazolin-3-ylmethyl)-benzoic acid;

or a pharmaceutically acceptable salt thereof, or an N-oxide thereof.

4. The combination of Claim 1, wherein the compound of Formula (A) is selected from:

15 4-{6-[3-(4-methoxy-phenyl)-prop-1-ynyl]-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl}-benzoic acid methyl ester;

4-[1-methyl-2,4-dioxo-6-(3-phenyl-prop-1-ynyl)-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid;

20 4-{6-[3-(4-methoxy-phenyl)-prop-1-ynyl]-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl}-benzoic acid;

4-{6-[3-(4-methoxy-phenyl)-prop-1-ynyl]-1-methyl-2,4-dioxo-1,4-dihydro-2H-pyrido[3,4-d]pyrimidin-3-ylmethyl}-benzoic acid;

4-[1-methyl-2,4-dioxo-6-(3-phenyl-prop-1-ynyl)-1,4-dihydro-2H-pyrido[3,4-d]pyrimidin-3-ylmethyl]-benzoic acid;

25 4-benzyl-7-(3-phenyl-prop-1-ynyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one;

4-benzyl-7-[3-(4-methoxy-phenyl)-prop-1-ynyl]-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one;

30 4-{7-[3-(4-methoxy-phenyl)-prop-1-ynyl]-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl}-benzoic acid methyl ester;

4-[5-oxo-7-(3-phenyl-prop-1-ynyl)-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl]-benzoic acid; and

4-(1-methyl-2,4-dioxo-6-(2-phenylethynyl)-1,4-dihydro-2H-quinazolin -3-ylmethyl)-benzoic acid.

5. A pharmaceutical composition, comprising a combination of valdecoxib, or a pharmaceutically acceptable salt thereof, and an allosteric alkyne inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent, or excipient.
10. A method of treating a disease or disorder selected from cartilage damage, inflammation, arthritis, and pain in a mammal, comprising administering to the mammal a therapeutically effective amount of a combination of valdecoxib, or a pharmaceutically acceptable salt thereof, and an allosteric alkyne inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof.
15. 7. The method according to Claim 6, wherein the disease or disorder is rheumatoid arthritis.
8. The method according to Claim 6, wherein the disease or disorder is osteoarthritis.
20. 9. The method according to Claim 6, wherein the disease or disorder is joint inflammation.
25. 10. The method according to Claim 6, wherein the pain is joint pain.